REMARKS

Reconsideration of the present application in view of the following remarks is respectfully requested. Claims 1-7, 9-13, and 16-24 are pending.

Rejections Under 35 U.S.C. 103(a)

Claims 1-7, 9, and 16-24 stand rejected under 35 U.S.C. 103(a) as allegedly unpatentable over the LEUKINE® Sargramostim product insert, in view of U.S. Patent No. 5,217,954 (Foster *et al.*) and U.S. Patent No. 6,620,784 (Ferrara *et al.*) and in the case of claims 4-8, further in view of U.S. Patent No. 5,545,536 (Kaushansky *et al.*) for reasons of record in the Office Action dated February 23, 2005. In addition, claims 10-13 stand rejected under 35 U.S.C. 103(a) as allegedly unpatentable over the LEUKINE® Sargramostim product insert, in view of U.S. Patent No. 6,620,784 (Ferrara *et al.*), U.S. Patent No. 5,217,954 (Foster *et al.*), and further in view of U.S. Patent No. 6,500,418 B1 (Dieckgraefe *et al.*) for reasons of record in the above-noted previous Office Action.

Applicants respectfully traverse this ground of rejection. As indicated in the response filed August 18, 2005, Applicants believe that a *prima facie* case of obviousness has not been established. Further, even assuming *arguendo* that a *prima facie* showing has been made, Applicants respectfully submit that the following rebuttal evidence and arguments are sufficient to overcome the same. In particular, the formulations of this invention possess unexpected properties sufficient to rebut a *prima facie* case. To this end, submitted herewith is a Declaration by Dr. Catherine Scholz, evidencing that formulations of this invention exhibit a double-peak absorption profile after subcutaneous administration, which enables not only an initial faster absorption of GM-CSF after subcutaneous injection, but also a subsequent sustained GM-CSF concentration in systemic circulation.

More specifically, the pharmacokinetic profile of a liquid formulation of sargramostim with EDTA was compared with that of a reconstituted formulation from lyophilized sargramostim material without EDTA in two Phase I studies. The liquid formulation of sargramostim with EDTA (referred to as "sargramostim EDTA" in the Declaration) contained 500 μg/ml sargramostim, 1.9 mg/ml (*i.e.*, 5.5 mM) EDTA, 1.15% benzyl alcohol, 40 mg/ml

mannitol, 10 mg/ml sucrose, and 1.2 mg/ml Tris (tromethamine), where the reconstituted formulation from lyophilized sargramostim material without EDTA (referred to as "sargramostim LY" in the Declaration) contained 500 μg/ml sargramostim, 0.9% benzyl alcohol, 40 mg/ml mannitol, 10 mg/ml sucrose, and 1.2 mg/ml Tris (tromethamine). The latter formulation is identical to the LEUKINE® liquid described in the primary prior art reference cited in the Office Action (*i.e.*, LEUKINE® Sargramostim product insert) except the minor difference in the concentrations of benzyl alcohol (0.9% benzyl alcohol in the reconstituted formulation from lyophilized sargramostim material vs. 1.1% benzyl alcohol in the LEUKINE® liquid formulation).

The liquid formulation of sargramostim with EDTA showed a unique pharmacokinetic profile consisting of a double-peak absorption profile and a decreased time to maximum serum concentration (*see*, Exhibits 2, 3, 4, 5, and 6 attached to the Declaration). During the initial absorption phase, sargramostim concentrations rapidly increased, reaching peak serum concentration at 0.25 hour post injection. The first rapid absorption peak was followed by a slower absorption phase where maximum sargramostim serum concentration (Cmax) was achieved at 2.5 hours post injection. The slower absorption phase allowed for sustained detectable levels throughout 12 to 24 hours post administration. In contrast, the reconstituted formulation from lyophilized sargramostim material without EDTA demonstrated only the single, slower absorption process, reaching a mean (geometric) C_{max} of 2.96 ng/ml at 4 hours post injection (*see*, Exhibits 2 and 3). The double-peak absorption associated with the sargramostim formulation containing EDTA did not appear to be dose dependent, nor influenced by ethnicity (*see*, Exhibits 4 and 5).

The unique double-peak pharmacokinetic profile of the liquid formulation of sargramostim with EDTA after subcutaneous administration is advantageous: It combines rapid initial absorption typically seen after intravenous administration of sargramostim formulations with subsequent slower absorption typically seen after subcutaneous administration of sargramostim formulations. The rapid initial absorption allows for sargramostim to be available earlier in systemic circulation and to elicit an earlier clinical benefit, whereas the following slower absorption phase allows for sustained sargramostim concentration in systemic circulation for a longer period of time (*e.g.*, 12-24 hours) post administration.

Accordingly, even assuming that a *prima facie* case has been made, Applicants respectfully submit that the unexpectedly advantageous properties for GM-CSF formulations with EDTA are sufficient to overcome the same, and request that this ground of rejection be withdrawn.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Applicants believe that all of the claims remaining in the application are now allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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Enclosures:
Declaration of Dr. Catherine Scholz
Exhibits 1-6

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